Seresto Evaluation - EPA Meeting

06 Apr 2021

Contains Confidential Business Information

Elanco

ATTENDEES

EPA

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Director, Veterinary Services & Senior Veterinary Toxicologist

Introductory Remarks

Slides 3-8 are presented by

Jennifer Schofield, DVM, CPH
Principal Scientist Regulatory Affairs
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TOPICS TO BE COVERED

- Insights into the documents submitted to the Congressional Subcommittee
- Address EPA's questions from our meeting 23 MAR 2021
- Brief overview of the data analysis EAH feels may be of assistance in EPA’s review
- Next steps

Seresto has a positive Benefit/Risk profile with a compelling Weight of Evidence in support of its Safety Profile.

There is no new data or validated safety signal indicating a change in Benefit/Risk.

- **Seresto´s safety profile is known and remains favorable; there is no scientific, medical or regulatory/legal reason to change the label.**
  - **Number of incident reports and death reports are not unique for Seresto.**
    They are in line with Open FDA data for other antiparasitic actives.
  - **>92% of all incident reports involved non-serious effects such as dermatologic application site disorders.**
    This is consistent with product support inquiries including responses to labeled side effects.
  - **Incident Reporting Rate for death, convulsions, and epileptic seizure < 1/10,000 and decreasing**
  - **No signal in disproportionality analysis for death, convulsion, epileptic seizure compared to Elanco portfolio**
  - **12 death reports classified probable / possible product related out of Ex. 4 CBI collars distributed (10 reports of entrapment)**
  - **Toxicological profile of the actives does not indicate potential for convulsions / epileptic seizures or death in the target animals**
  - **No serious neurological signs or fatalities observed in overdose/ingestion scenario**
  - **Systemic exposure with this topical slow-release product is very low and below lowest toxic levels.**
    Tissue levels are even lower, particularly in CNS due to blood brain barrier.
    Time to onset of neurological signs is inconsistent with peak plasma levels.

- **Background prevalence of death, seizures/convulsions provides more plausible alternative explanations**

- **Repeated proactive data and medical expert assessments – internally, by independent third parties such as SCI/PPH, and by regulators around the world – support positive Benefit/Risk profile.**

Insights into the documents submitted to the Congressional Subcommittee

Seresto PV Internal Investigation 2021.pdf
[2_EAH-HOR-00000035_VOL001.pdf]

Seresto animal safety review 2012-2015 from SafetyCall Feb23,2018 – FINAL REPORT.pdf
[4_EAH-HOR-00000095_VOL001.pdf]

Seresto PMS for human SAERs 2013-2015 FINAL 011418.pdf
[5_EAH-HOR-00000218_VOL001.pdf]

EPA’s Questions

EPA QUESTIONS

- Perceived high number of incident reports and overall incident reporting rate
- Was a PRR analysis performed for Seresto in the Elanco database?
- Are convulsions the second-most frequent PT of the Neurologic SOCs for other products in the Elanco portfolio?
- Was the time to onset for convulsions investigated?
- Is a change in labeling warranted?
  (e.g., with respect to serious neurological signs)
- How to further evaluate the ~1,700 death reports?

EAH Internal Analyses

Slides 10-34 are presented by

Dr. Niels Krebsfaenger, MBA, MDRA, DABT, ERT
Executive Director, Global Pharmacovigilance
Elanco Animal Health

Adverse Event Reporting (AER):

Number of Reports and >1/10,000 “Trigger”

Pharmacovigilance – WHO Definition

https://www.who.int/teams/regulation-prequalification/pharmacovigilance

"Pharmacovigilance" (PV) is the **science** and activities relating to the detection, **assessment, understanding** and prevention of adverse effects or any other drug related problem.

Its aims are to **enhance patient care and patient safety** and to support public health programmes by providing **reliable, balanced information** for the effective assessment of the **benefit-risk profile** of medicines and vaccines.

Adverse Event Reports (AERs)
Require medical expert assessment and prone to profound reporting bias

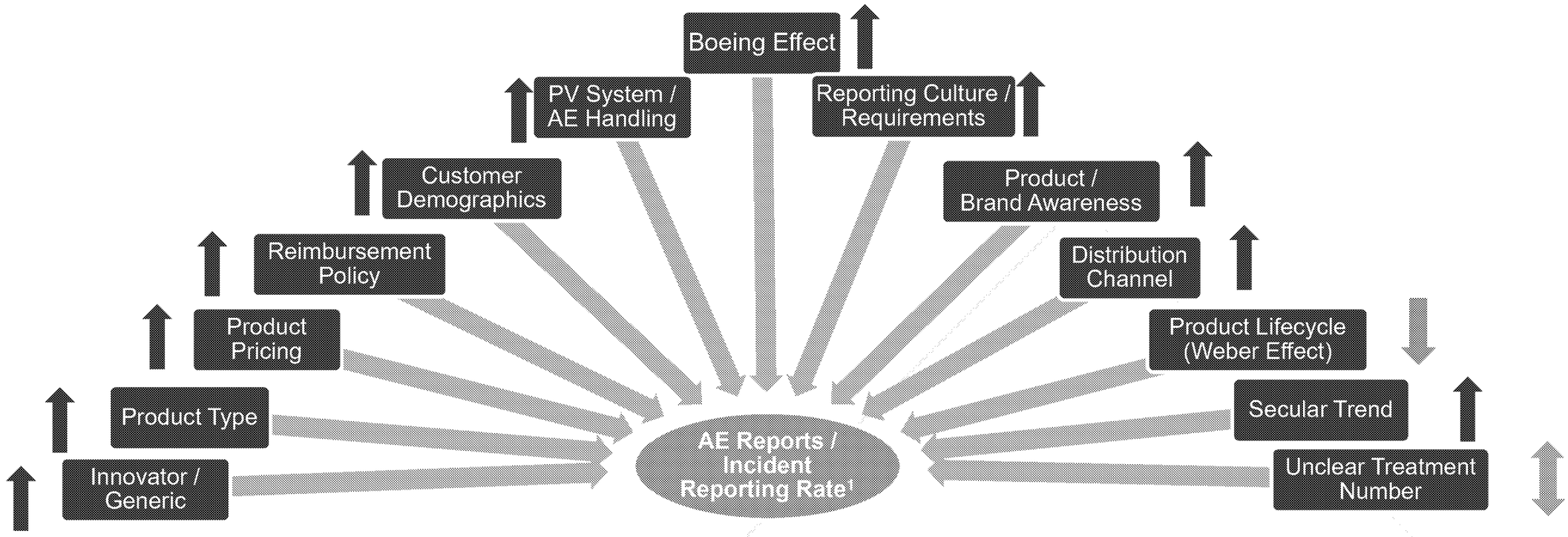
- As with product reviews found in online retailer websites, anyone can call, email, post, … about a perceived product issue
- Thus, AERs *per se* can be anecdotal rather than reliable medical information and profoundly biased:
  - PR Notice 98-3: "*An overview of the incident data simply identifies where there might be problems and serves as the first step in a process of gathering more information about the products or chemicals.*", "*Submission of an incident report by a registrant is not considered to be an admission of causation.*"
  - FDA[1]: "*An API dataset query result cannot be used to estimate the risk associated with the product or compare one drug or device product with another.*"
  - FDA[2]: *"However, there are limitations to the data and it is important to note that the information in both openFDA.gov and the CVM AER system is as reported to the FDA, and the agency has not necessarily determined if the products in question were the actual cause of the events being reported"*
- Further investigation and medical expert assessment is a prerequisite to drawing any conclusions, e.g.:
  - Data quality?
  - Causality?
  - Severity/Seriousness?
  - …
- This assessment is a core activity of pharmacovigilance experts in pharmaceutical companies as well as regulatory authorities.
- The safety of Seresto®, and all our products, is our number one priority at Elanco. We evaluate all AERs received according to local and international requirements and scientific standards (i.e., very similar to AE reports for human medicines).

1 https://www.fda.gov/animal-veterinary/product-safety-information/adverse-event-reports-animal-drugs-and-devices
2 https://www.fda.gov/news-events/press-announcements/fda-takes-new-steps-increase-access-adverse-event-report-data-medical-products-used-animals

REPORTING BIAS

Independent of product safety profile

PR Notice 98-3 "*It should be noted that staff members in EPA's Office of Pesticide Programs (OPP) have many years of experience processing and analyzing incident data, and are well aware of the vagaries of incident reports, such as the frequent lack of specific details, uncertainties of causality, the sometimes erroneous assumptions of reporters, etc. The Agency is also aware that large numbers of incident reports may simply reflect a large product sales volume or the existence of toll-free 800 numbers on product labels, making incident reporting easier.*"



- These impact factors are NOT related to product safety
- Several of these factors are expected to lead to a higher reporting rate for Seresto in the US – independent of the actual safety profile

Selected examples from diverse sources, e.g.: Amery, 1999, pp. 147-150; Bortnichak and Dai, 1999, pp. 457-461; Hodge, 2009, pp. 262-264;
[1]Incident Reporting Rate (the number of incident reports received based on sold treatments in the same period) as opposed to the Incidence Rate (the number of cases occurring in the real world based on treated animals – which is unknown).

High absolute number of Adverse Event Reports? Example Human Medicinal Products (FDA: FAERS & Open FDA)

https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard

"Importantly, the FAERS data by themselves are not an indicator of the safety profile of the drug or biologic. Some additional limitations to note include:

- **Duplicate and incomplete reports are in the system**: There are many instances of duplicative reports and some reports do not contain all the necessary information.
- **Existence of a report does not establish causation**: For any given report, there is no certainty that a suspected drug caused the event. While consumers and healthcare professionals are encouraged to report adverse events, the event may have been related to the underlying disease being treated with, or caused by, some other drug being taken concurrently, or occurred for other reasons. The information in these reports reflects only the reporter's observations and opinions.
- **Information in reports has not been verified**: Submission of a report does not mean that the information included in it has been medically confirmed nor it is an admission from the reporter that the drug caused or contributed the event.
- **Rates of occurrence cannot be established with reports**: The information in these reports cannot be used to estimate the incidence (occurrence rates) of the events reported.
- Patients should talk to their doctor before stopping or changing how they take their medications."

OpenFDA (HMPs): 5 most frequently reported active ingredients; 01 Jan 2013 - 31 Dec 2020

Active Ingredient	Number of Records
ASPIRIN	356,436
ADALIMUMAB	324,149
ETANERCEPT	308,170
ACETAMINOPHEN	243,229
PREDNISONE	221,115

FDA Adverse Events Reporting System (FAERS) Public Dashboard

U.S. FOOD & DRUG ADMINISTRATION

Home | Search | COVID-19 EUA | Resources | Submissions | Report Problem | FAQ

Total Reports 21,415,455

Serious Reports (excluding death) 11,897,872

Death Reports 2,058,612

Reports by Report Type

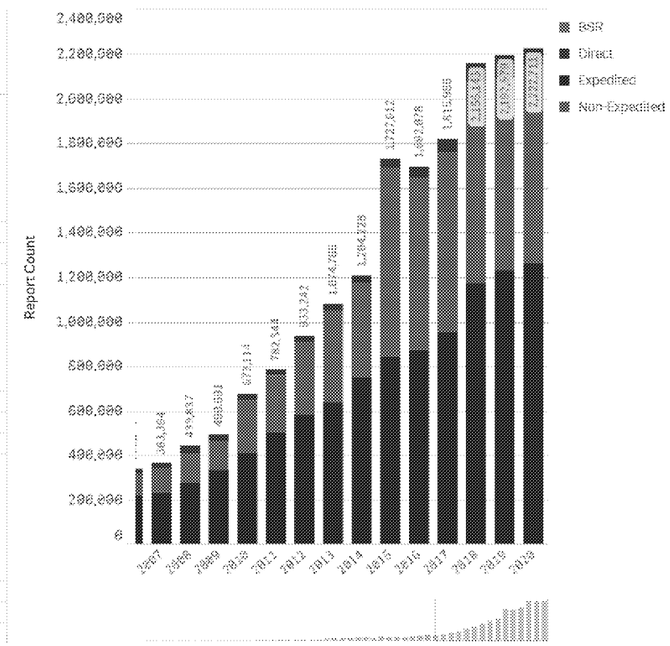
Since 1968 | Last 10 years

Reports received by Report Type

Year | Report Type

	Total Reports	Expedited	Non-Expedited	Direct	BSR
Total Reports	21,415,455	11,491,126	8,888,896	1,034,578	862
2020	2,222,711	1,258,211	825,941	78,559	-
2019	2,192,579	1,228,203	858,986	105,388	-
2018	2,156,143	1,168,443	900,149	87,551	-
2017	1,815,986	956,517	803,448	62,829	-
2016	1,692,878	879,143	770,044	50,691	-
2015	1,727,612	839,272	846,687	41,652	-
2014	1,284,128	746,261	473,737	34,230	-
2013	1,074,786	654,991	411,405	28,389	-
2012	933,242	577,647	326,580	29,015	-
2011	782,344	499,872	255,730	26,742	-
2010	673,114	409,499	234,671	28,944	-
2009	496,691	338,363	126,172	34,156	-
2008	439,837	274,255	132,686	32,896	-
2007	363,394	229,959	110,404	23,031	-
2006	335,740	219,709	95,557	20,474	-
2005	321,910	212,114	84,482	25,309	5
2004	272,864	161,359	89,243	21,657	5
2003	225,243	143,663	58,615	22,952	13
2002	184,809	127,778	36,644	20,447	20
2001	203,222	113,694	78,176	19,299	53
2000	198,812	94,166	88,176	16,120	350
1999	224,383	88,987	127,057	16,175	169
1998	188,898	78,819	73,681	15,247	143
1997	198,245	37,713	144,263	16,205	64
1996	172,211	26,312	130,310	15,569	20

Reports received by Report Type



Data as of December 31, 2020

This page displays the number of adverse event reports received by FDA for drugs and therapeutic biologic products by the following Report Types.

- Direct Reports are voluntarily submitted directly to FDA through the MedWatch program by consumers and healthcare professionals.
- Mandatory Reports are submitted by manufacturers and are categorized as:
  - i. Expedited reports that contain at least one adverse event that is not currently described in the product labeling and for which the patient outcome is serious, or
  - ii. Non-expedited reports that do not meet the criteria for expedited reports, including cases that are reported as Serious and expected, Non-serious and unexpected and Non-serious and expected.
- BSR Reports are 15-day Biologic Safety Reports which were submitted to FDA as a separate report type until 2005.

High absolute number of Adverse Event Reports?
Example Veterinary Medicinal Products (FDA: CVM AER & Open FDA)

https://www.fda.gov/news-events/press-announcements/fda-takes-new-steps-increase-access-adverse-event-report-data-medical-products-used-animals

"However, there are limitations to the data and it is important to note that the information in both openFDA.gov and the CVM AER system is as reported to the FDA, and the agency has not necessarily determined if the products in question were the actual cause of the events being reported."

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Ex. 4 CBI

Seresto US:

Ex. 4 CBI

IRR >1:10,000
Potential Trigger for Investigation but NOT an Absolute Threshold

- Applied to individual sign, not for all AE reports for a product overall
- An incident reporting rate >1:10,000 is generally not regarded as a serious safety concern.
- There is no US guideline suggesting a 1:10,000 threshold. EU and AU guidelines propose an incident reporting rate of 1:10,000 as a **potential trigger for further investigation**.[2, 3]
- Such investigation **may or may not validate a safety signal** that **may or may not lead to regulatory action / mitigation measures**.[2, 3]
- Rather, regulatory decision making is based on:
  - **individual case assessment** (causality, seriousness, …) by veterinarians
  - **weight of evidence**
  - **benefit / risk balance**

[1]EMEA/CVMP/900/03 – FINAL
[2]https://apvma.gov.au/node/314

Most detected potential signals are not confirmed

For example, in human medicinal products, out of 1,806 potential signals detected by EMA in 2019, only 97 (~5%) were actually confirmed and warranted further actions, i.e., **~95% of detected potential signals were not confirmed by regulators**

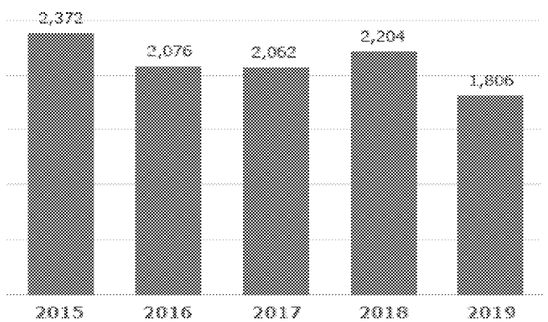
Signal detection

A safety signal is information on a new or known adverse event that is potentially caused by a medicine and warrants further investigation. Signals are generated from several sources, such as spontaneous reports of suspected adverse reactions, clinical studies and the scientific literature. The evaluation of a safety signal is a routine pharmacovigilance activity to establish whether there is a causal relationship between a medicine and a reported adverse event.

In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary. This mainly comprises changes in the information on medicines available for patients (in the package leaflet) and prescribers (in the summary of product characteristics).

In 2019, 1,806 potential signals were reviewed by EMA, approximately 78% of which originated from monitoring the EudraVigilance database, highlighting its central role for safety monitoring. This represents a decrease of 18% compared to 2018, where the number of signals assessed was particularly high. There was a small drop in the number of signals validated by EMA and assessed by the PRAC (50 signals in total), but a slight increase in the signals which were validated by Member States (46). In addition to signal detection activities and assessments at PRAC level, experts from the NCAs, in collaboration with EMA, provided a major contribution to the development of signal detection methods and continuous process improvement.

Signal reviewed by EMA



OUTCOME OF SIGNAL ASSESSMENT

1,806 potential signals reviewed by EMA

↓

97 confirmed signals were prioritised and assessed by the PRAC

Of these, 50 signals were detected and validated by EMA

46 signals were detected and validated by EU Member States

↓

Out of 97 confirmed signals

↓ 35 signals led to a product information update; 3 of these also included a Direct Healthcare Professional Communication (DHPC) to highlight important new safety information to prescribers

↓ 28 signals led to a recommendation for routine pharmacovigilance

↓ 33 signals were still under review by the PRAC at the end of 2018 as further data were required

↓ 1 signal led to a referral procedure to further investigate the issue

Source: EMA Annual Report 2019, p 69

Post-market surveillance systems should facilitate AE reports, and not be designed to limit AE reporting.

- Elanco operates a sensitive, best practice post market surveillance system with a 24/7 toll-free call center, e-reporting, etc. to ensure and facilitate responsible product stewardship.

- This will result in significantly higher reporting compared to less accessible systems.

- Importantly, to enable data-driven decision making,
  - downstream individual case assessments by medically trained personnel and
  - scientific signal detection and management processes need to be available, and
  - spontaneous reporting needs to be considered in an overall weight of evidence approach.

Disproportionality Analysis (DPA)

Quantitative Signal Detection: Disproportionality Analysis
Background & Data Analysis Approach

- **The objective of DPA is to identify statistically prominent reporting associations between pairs of products and events within Spontaneously Reported System (SRS) databases**
  - What is statistically prominent is determined by what might be expected by chance
  - The background for comparison is all other product and event combinations in the database
  - A finding of a statistic of disproportionate reporting (SDR) does not mean that a signal of suspected causality exists
- **Statistics in common use in DPA include PRR, ROR, BCPNN, and MGPS with associated thresholds** (i.e., signal detection algorithms)
- **Important to the application of DPA within an SRS database is performance testing against a standard**, generally focusing on precision and sensitivity

References:

1. Almenoff J, Tonning JM, Gould LA, et al. Perspectives on the use of quantitative signal detection in pharmacovigilance. Drug Safety; 28 (11):981-1007, 2005.
2. Bate A, Lindquist M, Edwards IR, et al. A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol 54:315-321, 1998.
3. CIOMS Working Group VIII. Practical Aspects of Signal Detection in Pharmacovigilance. The Council for International Organizations of Medical Sciences. Geneva. 2010.
4. Guideline on good pharmacovigilance practices (GVP). Module IX- Signal management (Rev 1). Heads of Medicine Agencies, European Medicines Agency. EMA/827661/2011 Rev 1. 09 October 2017.
5. Hauben M, Madigan D, Gerrits CM, et al. The role of data mining in pharmacovigilance. Expert Opin Drug Saf; 4 (5): 929-948, 2005.
6. Novotny MJ. Spontaneous reporting system databases, data mining, and disproportionality analysis. In: Proceedings of the 17th Biennial AAVPT Symposium of the American Academy of Veterinary Pharmacology and Therapeutics, Madison WI. May 2011.
7. Novotny MJ. Disproportionality Analyses in Animal Health SRS Databases: Challenges. 9th Biennial Conference on Signal Detection and Interpretation in Pharmacovigilance. Drug Safety Research Unit. 8 June 2017.
8. Recommendation on pharmacovigilance surveillance and signal detection of veterinary medicinal products. EMA/CVMP/PhVWP/ 901279/2001. 13 May 2015.
9. Wisniewski AFZ, Bate A, Bousquet C, et al. Good signal detection practices: evidence from IMI PROTECT. Drug Safety; 39:469-490, 2016.
10. Candore, G., Juhlin, K., Manlik, K., Thakrar, B., Quarcoo, N., Seabroke, S., & Slattery, J. (2015). Comparison of statistical detection methods within and across spontaneous reporting databases. *Drug Safety*, *38*, 577–587.
11. Novotny MJ, Rhodes A, Shields J, et al. (2021). Evaluation of signal detection algorithms within the Elanco Animal Health Pharmacovigilance database. J Vet Pharmacol Therap, 44(1):107-115.

Seresto Disproportionality Analysis
Background, Data Analysis Approach, Conclusion

- All products and all events across the two legacy companies' SRS databases by species
  - 652,084 canine cases
  - 175,554 feline cases

- Analyses performed at the generic product, VeDDRA Preferred Term, and case levels

- Results presented for the points estimates and confidence intervals for PRR and BCPNN

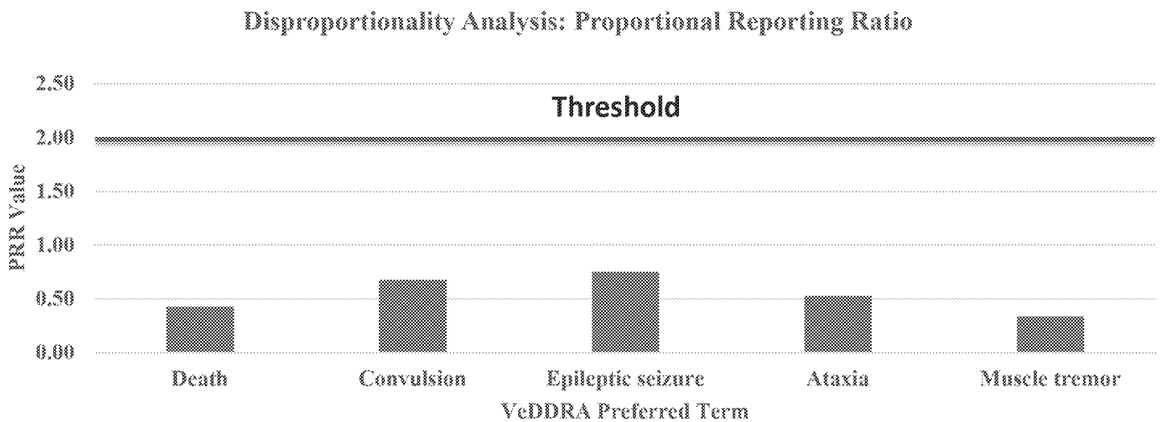
- Based on performance testing of the Elanco SRS database, the BCPNN statistic is superior to others in terms of precision, sensitivity, and other performance measures (Novotny, *et al.*, 2021)

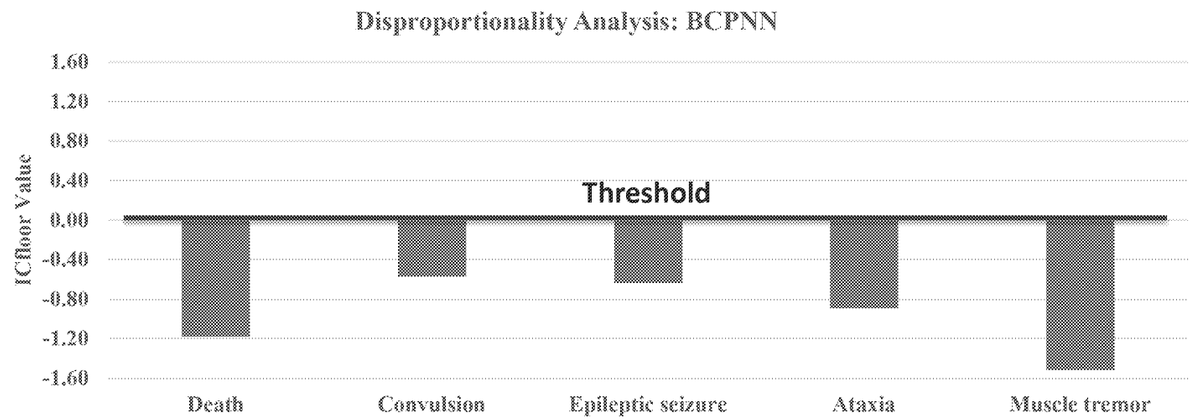
For both, dog and cat,
preferred term (PT) Death, Convulsions, Epileptic seizures, Ataxia and Muscle tremor
were NOT disproportionally reported for Seresto,
i.e., they report within background

Novotny MJ, Rhodes A, Shields J, et al. (2021). Evaluation of signal detection algorithms within the Elanco Animal Health Pharmacovigilance database. J Vet Pharmacol Therap, 44(1):107-115.

Seresto Disproportionality Analysis in Elanco Portfolio

No Alert in PRR or ICf / BCPNN for Seresto **Dog** PT Death, Convulsion, Epileptic Seizure, Ataxia, Muscle Tremor



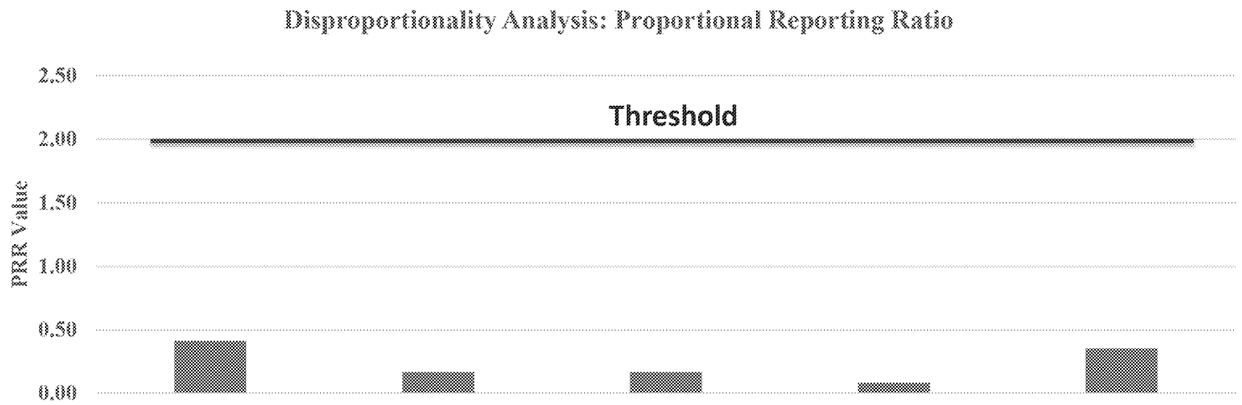


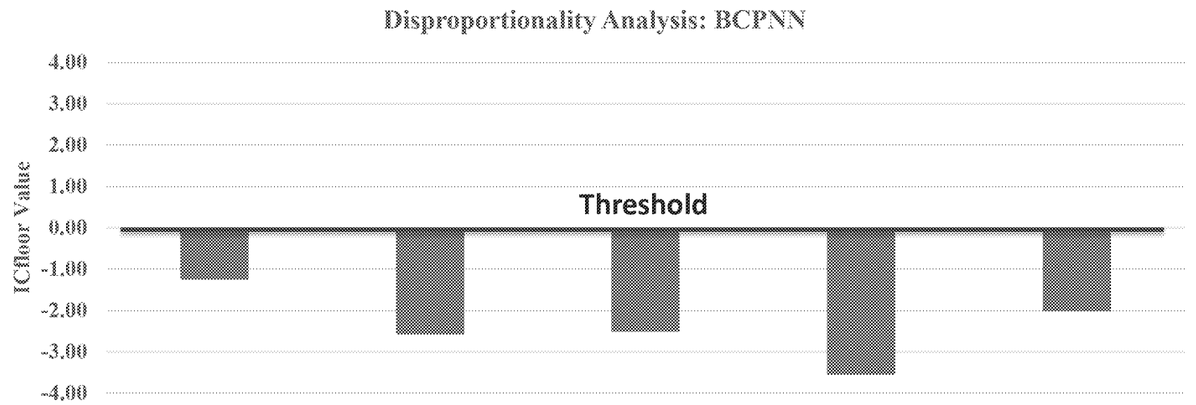
Product	VeDDRA Preferred	A			B			C			D			Denominator Total	PRR025	PRR	PRR975	PRR Alert	ICfloor	IC	ICceiling	IC Alert
		Elanco	Bayer	Total	Elanco	Bayer	Total	Elanco	Bayer	Total	Elanco	Bayer	Total									
Imidacloprid + Flumethrin	Death	0	1.275	1.275	6	94.145	94.151	12.473	4.895	17.368	389.925	149.365	539.290	Ex. 4 CBI				No	-1,1786	-1,0969	-1,0153	No
	Convulsion	2	1.598	1.600	4	93.822	93.826	10.429	3.371	13.800	391.969	150.889	542.858					No	-0,5671	-0,4940	-0,4209	No
	Ataxia	0	1.670	1.670	6	93.750	93.756	12.534	5.917	18.451	389.864	148.343	538.207					No	-0,8895	-0,8179	-0,7463	No
	Muscle tremor	0	1.011	1.011	6	94.409	94.415	10.561	6.955	17.516	391.837	147.305	539.142					No	-1,5139	-1,4224	-1,3309	No
	Epileptic seizure	0	105	105	6	95.315	95.321	522	292	814	401.876	153.968	555.844					No	-0,6362	-0,3556	-0,0751	No

- Seresto **Dog** PT Death, Convulsions, Epileptic Seizures, Ataxia and Muscle Tremor do NOT report disproportionally in the Elanco portfolio, i.e., they report within background

Seresto Disproportionality Analysis in Elanco Portfolio

No Alert in PRR or ICf / BCPNN for Seresto **Cat** PT Death, Convulsion, Epileptic Seizure, Ataxia, Muscle Tremor





Product	VeDDRA Preferred	A			B			C			D			Denominator Total	PRR025	PRR	PRR975	PRR Alert	ICfloor	IC	ICceiling	IC Alert
		Elanco	Bayer	Total	Elanco	Bayer	Total	Elanco	Bayer	Total	Elanco	Bayer	Total									
Imidacloprid + Flumethrin	Death	1	607	608	0	30.893	30.893	3.254	3.515	6.769	59.553	77.731	137.284	175.554	0,3783	**0,4107**	0,4460	No	**-1,2401**	-1,1214	-1,0027	No
	Convulsion	0	191	191	1	31.309	31.310	886	4.405	5.291	61.921	76.841	138.762	175.554	0,1429	**0,1651**	0,1907	No	**-2,5681**	-2,3588	-2,1496	No
	Ataxia	0	328	328	1	31.172	31.173	3.216	5.807	9.023	75.439	59.591	135.030	175.554	0,1490	**0,1662**	0,1855	No	**-2,5119**	-2,3515	-2,1912	No
	Muscle tremor	0	216	216	1	31.284	31.285	1.758	10.288	12.046	61.049	70.958	132.007	175.554	0,0717	**0,0820**	0,0938	No	**-3,5396**	-3,3427	-3,1458	No
	Epileptic seizure	0	15	15	1	31.485	31.486	72	124	196	62.735	81.122	143.857	175.554	0,2070	**0,3500**	0,5916	No	**-2,0086**	-1,2869	-0,5653	No

- Seresto **Cat** PT Death, Convulsions, Epileptic Seizures, Ataxia and Muscle Tremor do NOT report disproportionally in the Elanco portfolio, i.e., they report within background

Case Narrative - Examples

FURTHER ANALYSIS OF REPORTED DEATH CASES (2012 – 2015)

305 dog and 100 cat reports

57% - other causes for death/euthanasia were confirmed / reasonably assumed

- underlying condition, neoplasm, accident, etc.

42% no specific cause to explain the death or euthanasia, thereof:

- 63% of the pets were 10 years or older
- 45% of these animals were 13 years or older
- 23% were inquiries unrelated to the death of the animal

The clinical signs reported with death are highly variable and heterogeneous. If the effect would be product related, the signs would be expected to focus on one or very few clinical phenomena.

Various estimates exist for the US dog and cat population

- Similar estimates exist for the annual rate of death / euthanasia (millions of animals)
- Contributes to the potential for background noise being reported following the use of Seresto

Case narrative examples - death

USA-BAYERBAH-2014-US0019964

On 26Apr2014, an 18-month-old, 57 pound, neutered male, Plott hound canine, in unknown condition, with no known concomitant medical conditions, had the Seresto Large Dog (Flumethrin-Imidacloprid) collar placed around his neck by the owner.

On 10May2014 the dog was hit by a vehicle and passed away from unknown causes. A necropsy was not performed.

No further information expected. Case closed.

Case narrative examples - death

USA-BAYERBAH-2015-US0036338

On 01-Aug-2014, a 14-year-old, 40 pound, neutered male, Spaniel (English Cocker) canine, in poor condition, with a concomitant medical condition of diabetes, had 1 Seresto Large Dog collar (Flumethrin-Imidacloprid) placed around the neck by the owner.

On 14 Sept 2014, the dog was euthanized due to his poor health and age. No necropsy was performed.

The purpose of the call to Bayer Animal Health was not to report the death of this patient but to inquire about the use of the product on other dogs in the home.

No more information is expected. Case is closed.

Case narrative examples - death

USA-BAYERBAH-2017-US0022820

On an unspecified date in approximately 2016, an approximately 13-year-old, male cat, of unknown signalment and condition, with concomitant medical conditions of unspecified heath conditions, who lived indoors and outdoors, had 1 Seresto Cat (Flumethrin-Imidacloprid) collar placed around the neck by the animal owner.

On approximately 29 Mar 2017, the cat died. It is unknown if the cat was examined by a veterinarian. No known necropsy was performed.

Limited information was obtained at the time of the communication. Further attempts to gather additional information will not be made. The reporting party contacted Bayer Animal Health to inquire about reimbursement for another pet and not to report the death of this animal.

No further information is expected; the case is closed.

CONFIRMED COUNTERFEIT REPORTS

- Further to the discussion on background, there are a number of cases submitted to EPA that include confirmed counterfeit products
  - In 2020 alone, there are 2 reports of convulsions
  - Through 2020, there are 14 reports involving death

- While none of these specific confirmed counterfeit collars were tested, other collars with similar characteristics were tested
  - Many of the analyzed collars either had no or lower than expected presence of the correct active ingredients.
  - The Assay Flumethrin indicates, that in most cases no Flu was present.
  - Imidacloprid is either not present or below the level of specification.

“Rank Order” of PT Convulsion

“Rank Order” of PT Convulsions

Confirms no Signal in DPA

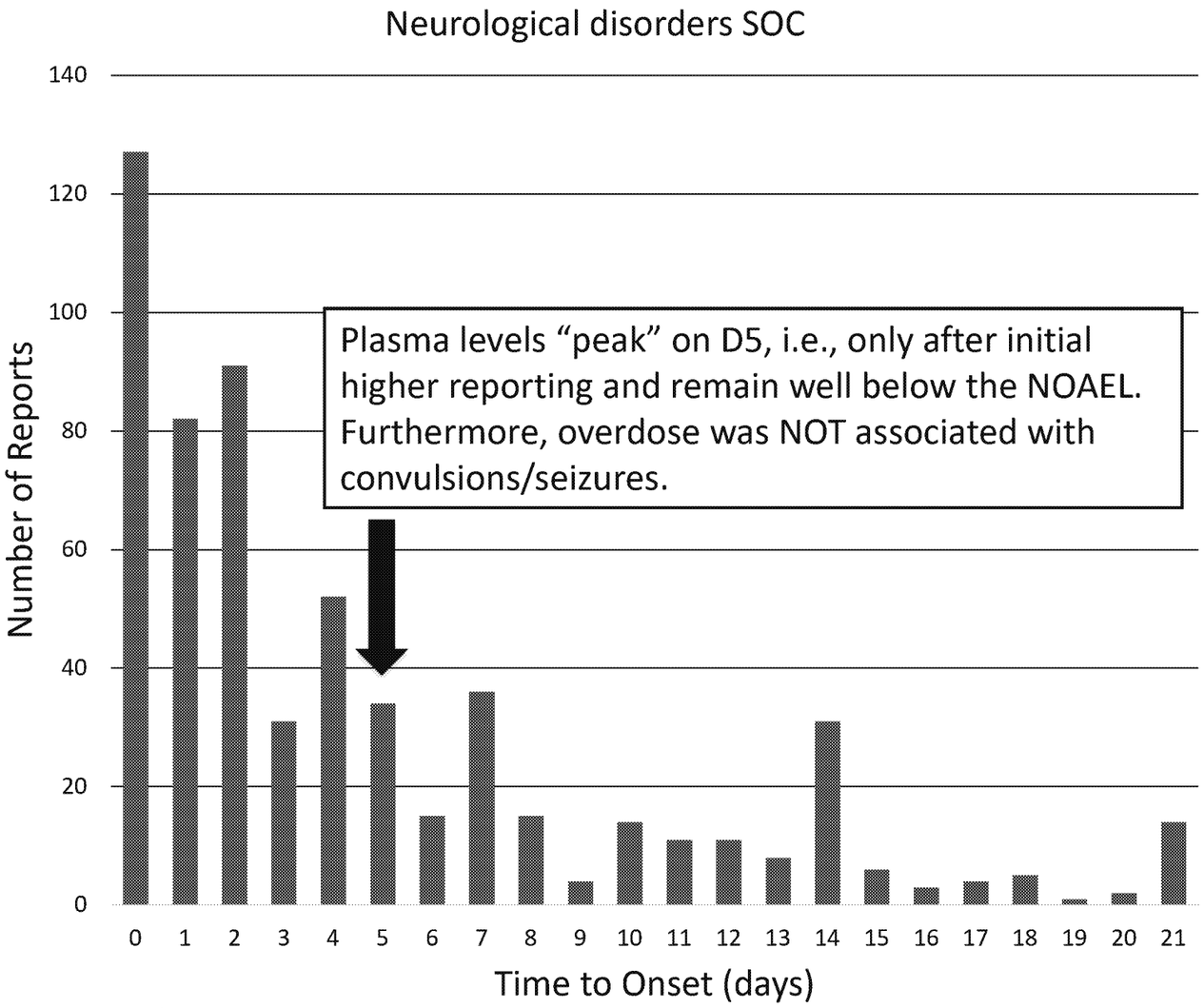
- Seresto:
  - Convulsions are the 2nd most common PT in the neurologic SOC specifically, with a 2020 rate of **Ex. 4 CBI** /10,000 collars distributed.
  - Convulsions are the 23rd most frequently reported PT overall for Seresto in 2020.
- Elanco Portfolio:
  - Legacy Elanco portfolio
    - 2nd most common PT in the neurological SOC (Jan 2015 – Mar 2021):
    - 12th (dog) and 27th (cat) most common PT overall (all data by end of 2020)
  - Legacy Bayer portfolio (2020)
    - 3rd most common PT in the neurological SOC
    - 23rd most common PT overall

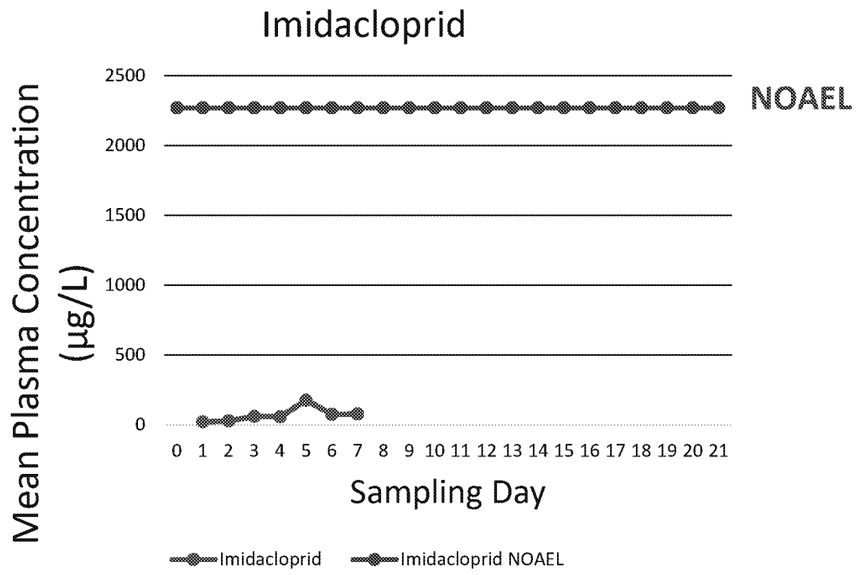
Systemic Exposure

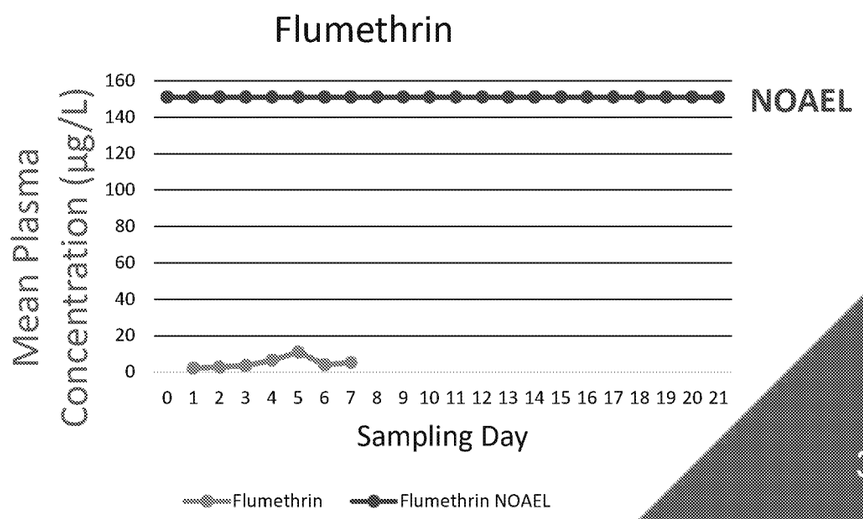
Time to Onset

Plasma kinetics demonstrate a lack of evidence for direct systemic toxicity

Time to Onset (days) of Neurologic SOC VeDDRA Terms Reported in the First 21 Days in Dogs vs Mean Plasma Concentration (µg/L) of Imidacloprid and Flumethrin (2019-2020)

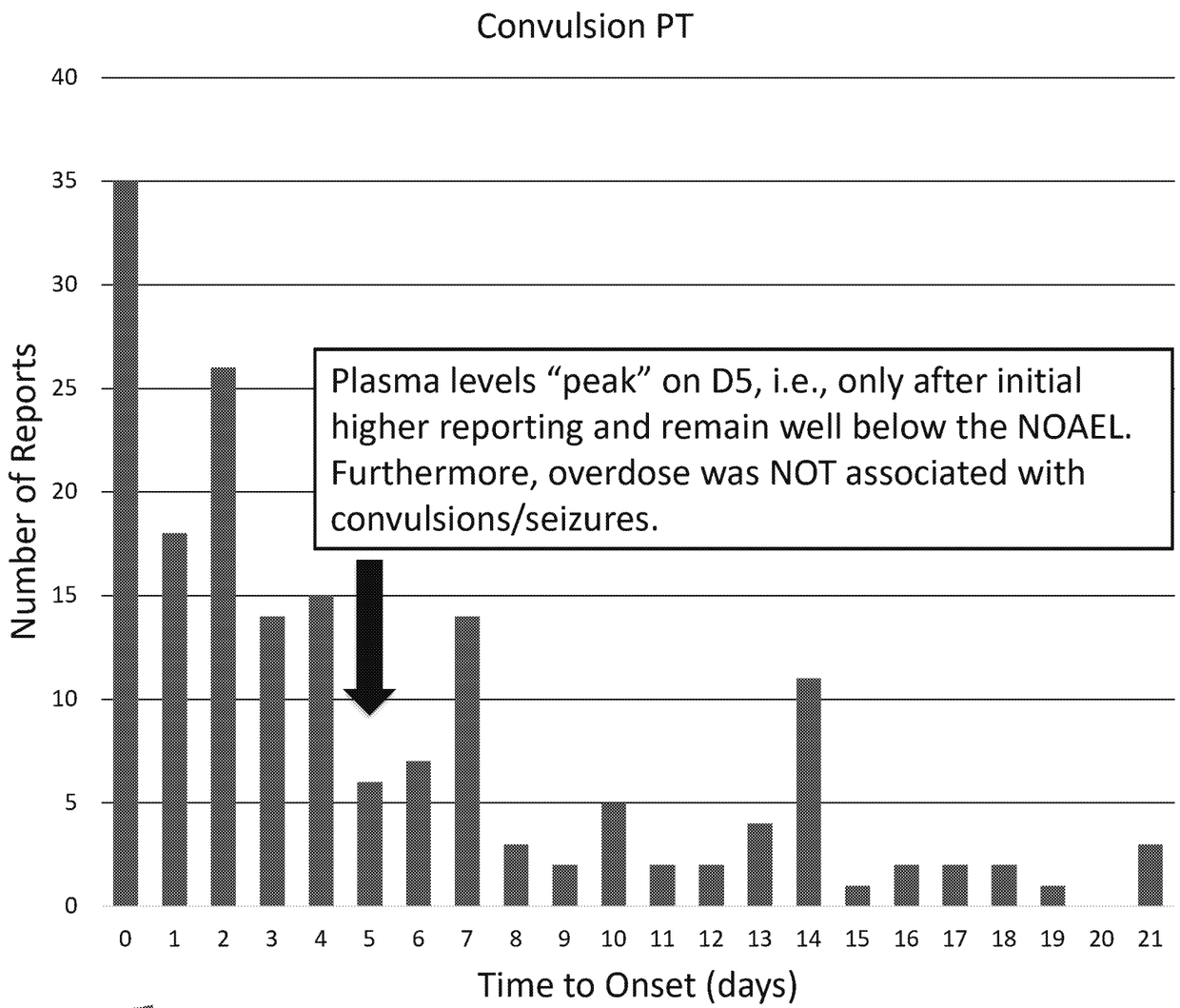


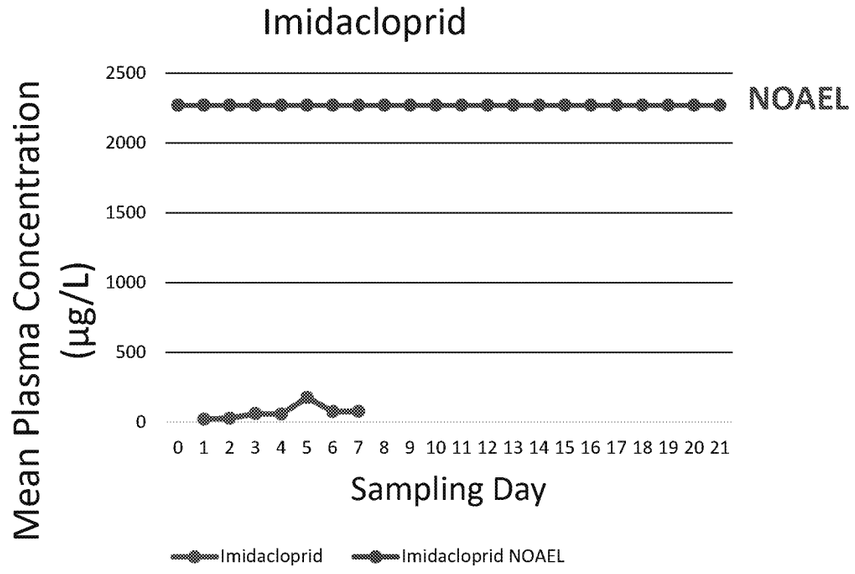


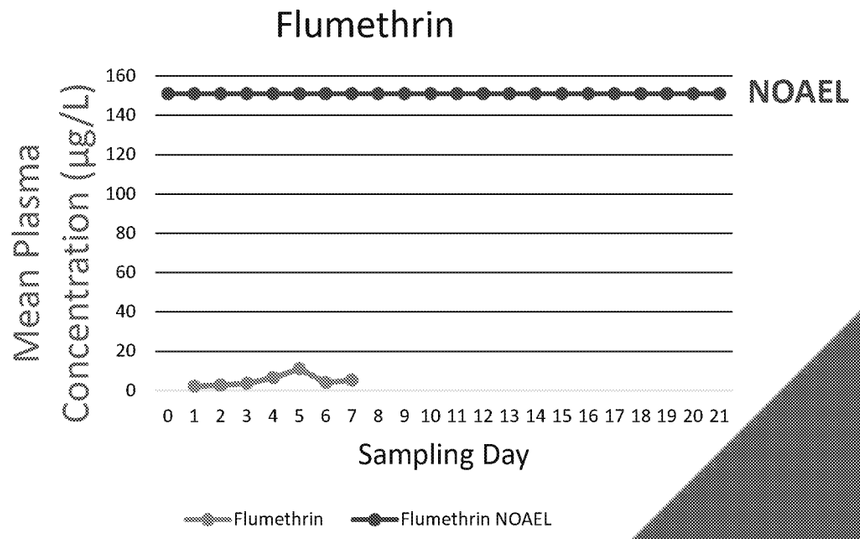


Plasma kinetics demonstrate a lack of evidence for direct systemic toxicity

Time to Onset (days) of Convulsions Reported in the First 21 Days in Dogs and Cats vs Mean Plasma Concentration (µg/L) of Imidacloprid and Flumethrin (2019-2020)







Weight of Evidence (WoE)

Is a change in labeling warranted?
(e.g., with respect to serious neurological signs)

How to further evaluate the ~1,700 death reports?

Slides 36-39 are presented by

SCI / PPH / U of MN
Rick Kingston, Pharm D
President, Regulatory and Scientific Affairs/Sr. Clinical Toxicologist
Ahna Brutlag, DVM, MS, DABT, DABVT
Director, Veterinary Services & Senior Veterinary Toxicologist

HHE
"Weight of Evidence" When Assessing Safety

Clinical Studies Public/ Proprietary

Spontaneous Reports to Regulators CPSC/EPA/FDA/ HC

Direct to Regulators Public/HCP

Direct to Manufacturer Domestic/ Foreign

- Consumers
- Health Professionals

Published Anecdotal Case Reports

Product / Ingredient Weight of Evidence Standard Factors of Association

- Expectedness
- Temporality
- Biological Plausibility
- De-challenge
- Re-challenge
- Confounding Factors

Basic Science / Toxicology Animal Data

NEISS/ER Data

Professional Medical Society Groups

Local Governmental / Health Authorities

NGO's e.g. Consumer Reports/CSPI/ NRDC

Poison Control Centers (Public & Industry)

SafetyCall INTERNATIONAL

PET POISON HELPLINE®

Weight of Evidence

Review of Data Streams and Reducing Bias (≥3 streams of data?)

- Only one of the typical safety/toxicity data streams is showing a potential safety signal (imperative to reduce bias in spontaneously reported AEs by separating higher and lower quality reports)
- Other data streams are silent or invalidating a safety signal
  - No published studies or clinical trials
  - No published anecdotal case reports
  - No professional society safety alerts
  - No local government or health authority raising concern over a safety signal based on specific data
  - No NGO is presenting “new” data supporting a safety signal
- One of the most sensitive surveillance systems (Public Poison Control Centers) is supporting Seresto’s Wide Margin of Safety (no validation of a safety signal)

SafetyCall INTERNATIONAL

PET POISON HELPLINE®

Weight of Evidence

Public Poison Control Centers

- Along with “direct from consumer” spontaneously reported adverse event incident data, one of the more “sensitive” systems of surveillance
- Contacted by consumers for acute emergency treatment and/or triage advice
  - Non-life threatening adverse effects and/or management of labeled side effects of a minor or more chronic nature are typically reported to the manufacturer or Industry poison center
- Routinely contacted by healthcare professionals managing serious or life-threatening adverse effects secondary to any suspected toxin, or excessive exposure to drug, chemical or other potential toxins

SafetyCall INTERNATIONAL

PET POISON HELPLINE®

No Seresto fatalities reported to Animal Poison Control

- 408 cases (2013 – March 2021)
  - Species: 97% canine, 3% feline
  - Route of exposure
    - Oral: 86%
  - **No fatalities**
  - Seizures
    - 3 cases, all unlikely association
    - e.g.: Dog had seizure 3-4 d after Seresto application. **Collar removed.** 10 d later has seizures again. Recommend neurology consult to look for other causes.

Clinical signs	Flumethrin & imidacloprid (Seresto)	
Vomiting	202	49.5%
Asymptomatic	152	37.3%
Lethargy	54	13.2%
Diarrhea	26	6.4%
Anorexia	26	6.4%
Ataxia	14	3.4%
Panting	7	1.7%
Agitated/irritable	6	1.5%
Vocalization	5	1.2%

All other clinical signs ≤ 1% cases

Conclusion: Ingestion has the highest risk of producing systemic toxicity. Even in this scenario, there were no fatalities and clinically significant adverse effects were rarely reported. The majority of reported effects were mild and self-limiting. In total >1/3 animals were asymptomatic.

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PET POISON HELPLINE®

Serious Neurological Disorder Reports
Weight of Evidence for no relation to active ingredients

- 1,738 reports of convulsions v[Ex. 4 CBI] collars sold in the US (2013-2020)
- **IRR for PT convulsion [Ex. 4 CBI] in 2020 (231 reports with [Ex. 4 CBI] collars sold)**
- IRR [Ex. 4 CBI] in 2020 (adjusted for animal months protected)
- **IRR decreasing since launch (Weber effect)**
- **Only 23 reports classified possible (B) product related; there were none considered probable (A)**
- **Toxicological profile of IMI and FLU does not indicate potential for convulsions / epileptic seizures in the target animals**
  - Tox studies up to MTD and TAS studies up to 5x performed in Beagles, a breed with higher prevalence / sensitivity for convulsions
- **No serious neurological signs observed in overdose situation**
  - 1x, 3x, 5x VICH TAS/CAS incl. more sensitive pediatric animals (6 studies)
  - PV data with chewing and/or ingestion of collar
    (2020: of 277 reports of collar ingestion, 263 “minor,” 14 “moderate” and of 74 reports of other oral exposure, 68 “minor,” 6 “moderate”, no “major” or “death”)
  - Pet Poison Helpline (PPH) database (2013-3/2021): 3 seizures out of 408 reports, coded as unrelated
- **Systemic exposure is very low and below NOAEL. Tissue levels even lower, particularly in CNS due to blood brain barrier.**
- **Time to onset: Higher reporting on D0-3, i.e., before API Cmax** (~D5, slow release) which is < NOAEL: no relation to APIs
- **No signal in disproportionality analysis** compared to ELANCO portfolio (PRR, ICf/BCPNN; PT Convulsion, PT Epileptic Seizure)
- **Background prevalence of seizures/convulsions in dogs (~0.2-2%) provides more plausible alternative explanations**
  - With [Ex. 4 CBI] collars sold in the US in 2020 (~2/3 dog), assuming only one epileptic episode would occur within the 8 months of duration, it would be **expected that** [Ex. 4 CBI] **epileptic seizures/convulsions** would occur with animals wearing the collar but independent of the collar (they would also have experienced epileptic episodes without wearing the collar)

➢ There is no established link between convulsions/seizures and Seresto

➢ There is no evidence for labelling convulsions/seizures based on the data, science, medical assessments, statistics, …

Death Reports
Weight of Evidence for no relation to active ingredients

- ~1700 reports with **Ex. 4 CBI** collars sold in the US (2013-2020)
- **IRR Ex. 4 CBI in 2020 (167 reports with Ex. 4 CBI collars sold)**
- IRR **Ex. 4 CBI** in 2020 (adjusted for animal months protected)
- **12 reports classified probable (A) or possible (B) product related out Ex. 4 CBI collars distributed, 10 of those entrapment**
- **Systemic exposure is very low and below NOAEL.** Tissue levels even lower, particularly in CNS due to blood brain barrier.
- **No fatalities observed in overdose situation**
  - 1x, 3x, 5x VICH TAS/CAS incl. more sensitive pediatric animals (6 studies)
  - PV data with chewing and/or ingestion of collar
    (2020: of 277 reports of collar ingestion, 263 “minor,” 14 “moderate” and of 74 reports of other oral exposure, 68 “minor,” 6 “moderate”, no “major” or “death”)
  - **No single death report in the Pet Poison Helpline (PPH) database**
- **No signal in disproportionality analysis** compared to ELANCO portfolio (PRR, ICf/BCPNN; PT death)
- **Background prevalence of death in dogs and cats (7-8%) provides more plausible alternative explanations**
  - With **Ex. 4 CBI** collars sold in the US in 2020 (~2/3 dog, ~1/3 cat, 8 months duration), it would be **expected that Ex. 4 CBI deaths Ex. 4 CBI** dogs and **Ex. 4 CBI** cats) would occur with animals wearing the collar but independent of the collar (they would also have died without wearing the collar)
  - Case narratives often indicate alternative cause like underlying disease, accident, inquiry, …

➢ There is no established link between death and exposure to the active ingredients contained in Seresto.
➢ There is no evidence for labelling death based on the data, science, medical assessments, statistics, …

Conclusions, Questions, Discussion and Next Steps

Seresto has a positive Benefit/Risk profile with a compelling Weight of Evidence in support of its Safety Profile.

There is no new data or validated safety signal indicating a change in Benefit/Risk.

- **Seresto´s safety profile is known and remains favorable; there is no scientific, medical or regulatory/legal reason to change the label.**
  - **Number of incident reports and death reports are not unique for Seresto.**
    They are in line with Open FDA data for other antiparasitic actives.
  - **>92% of all incident reports involved non-serious effects such as dermatologic application site disorders.**
    This is consistent with product support inquiries including responses to labeled side effects.
  - **Incident Reporting Rate for death, convulsions, and epileptic seizure < 1/10,000 and decreasing**
  - **No signal in disproportionality analysis for death, convulsion, epileptic seizure compared to Elanco portfolio**
  - **12 death reports classified probable / possible product related out of Ex. 4 CBI collars distributed (10 reports of entrapment)**
  - **Toxicological profile of the actives does not indicate potential for convulsions / epileptic seizures or death in the target animals**
  - **No serious neurological signs or fatalities observed in overdose/ingestion scenario**
  - **Systemic exposure with this topical slow-release product is very low and below lowest toxic levels.**
    Tissue levels are even lower, particularly in CNS due to blood brain barrier.
    Time to onset of neurological signs is inconsistent with peak plasma levels.

- **Background prevalence of death, seizures/convulsions provides more plausible alternative explanations**

- **Repeated proactive data and medical expert assessments – internally, by independent third parties such as SCI/PPH, and by regulators around the world – support positive Benefit/Risk profile.**